JOINT MEETING No. 1

Section of General Practice with Section of Medicine

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DISCUSSION ON THE USE AND ABUSE OF ANTIBIOTICS

Dr. David Wheatley: *Uses of Antibiotics*

Until recently, as far as the general practitioner was concerned, antibiotics could be divided into two groups, those which were freely prescribable and those which could only be obtained through the hospital service. In the first group are penicillin, streptomycin, chloramphenicol, erythromycin and the sulphonamides, for the last-mentioned are no less an antibiotic than the others and must be considered in conjunction with them. In the second group are the tetracyclines (Aureomycin, Terramycin and tetracycline itself), the polymyxins and a heterogeneous medley tailing off in practical usefulness. Erythromycin may be dismissed immediately except for the rare case of infection resistant to all the other antibiotics. When indicated, at the present time it is probably better to use an antibiotic from the second group in preference to erythromycin, because of the latter's strong capacity for inducing drug resistance. However, as in the case of penicillin, time may show this to be a false fear as far as general practice is concerned, but it must be remembered that erythromycin covers only the same bacterial spectrum as penicillin itself. Likewise there will be little indication to use streptomycin alone because of its ototoxicity, although the risk of the latter may be reduced by using a streptomycin-dihydrostreptomycin mixture. I am not including the treatment of tuberculosis as this is usually undertaken by the chest clinics. This leaves penicillin, the sulphonamides and chloramphenicol which have been our mainstay in general practice, until the recent release of the newer antibiotics.

Sometimes it may be expedient to combine two antibiotics, and here it should be remembered that antibiotics may be divided, roughly, into two groups. The first includes penicillin, the sulphonamides and streptomycin, all of which are synergistic with each other. The second group includes chloramphenicol, Aureomycin, Terramycin, &c., these also being synergistic one with the other. Members of one group, however, are antagonistic to members of the other and should not be combined.

As bacteriological examination may often be delayed, some reliance must be placed upon "blind" therapy. Table I shows some of the commoner bacteria with their degrees of sensitivity to different antibiotics.

TABLE I.—BACTERIAL SENSITIVITIES

	Sulphonamides	Penicillin	Streptomycin	Chloramphenicol	Aureomycin	Terramycin
Staph. aureus	+	++++	++	++	++	++
Str. hæmolyticus	+++	++++	−	++	+++	++
Pneumococcus	+++	++++	++	+++	+++	++
H. pertussis	−	−	−	++	?+	?+
Bact. coli	+++	−	+++	+++	++	+++
Bact. sonnei	+++	−	+	+++	++	+++
Neisseria	+++	++++	−	++	++	++
Proteus	−	−	+	+	−	?
Pseudomonas	−	−	?+	?+	?+	?

We are now in a position to decide which antibiotic or combination of antibiotics is most suitable for each infection and Table II shows some of the commoner conditions met with in general practice. In each case the antibiotic of choice is shown, together with the next most suitable one. If there is no response within thirty-six hours, the second choice should be substituted, or whatever other antibiotic may be indicated as a result of bacteriological examination and sensitivity tests.

Mode of administration.—Frequent injections are clearly impossible in general practice, therefore in the case of penicillin, reliance must be placed upon twelve- or twenty-four-hourly injections, or upon oral therapy. Hence we have here a major difference between domiciliary and hospital practice, as the widespread use of oral penicillin is almost entirely confined to general practice. Hence the general practitioner is in a more favourable position to form an opinion as to its effectiveness.

Three of the more common conditions are (1) Minor Pyogenic; (2) Acute Tonsillitis and Pharyngitis; (3) Acute Otitis Media.

TABLE II

(1) *Chest Diseases*				Carbuncles, boils, &c.	P	(C)
Pneumonia	P+S	(C)		Burns	P+Str. (topical)	(C)
Acute bronchitis	P	(S)	(6) *Obstetrics and Gynæcology*			
Pleurisy	P			Puerperal fever	P+S or Str.	
(2) *Infectious Diseases*				Mastitis (infective)	P	(S)
Dysentery	S	(C)		Vaginitis (bacterial)	S	(C)
Pertussis	C			Infected nipples	P+Str. (topical)	
Scarlet fever	P		(7) *Dermatology*			
Gonorrhœa	P			Cellulitis	P	(P+S)
(3) *Genito-urinary Infection*	S	(C)		Impetigo	P (topical)	
(4) *E.N.T. Infections*				Erysipelas	P	(P+S)
Acute otitis media and acute mastoiditis	P+S	(C)		Intertrigo	C	(P) (topical)
Chronic otitis media	C (topical)		(8) *Ophthalmic Conditions*			
Meatal boils	P			Conjunctivitis	P	(C)
Acute tonsillitis and quinsy	P	(S)		Blepharitis	P	(C) (topical)
Acute sinusitis	P			Corneal ulcers	P	
(5) *Minor Surgical Conditions*						
Hand infections	P	(C)				

Key

S=Sulphonamides C=Chloramphenicol P=Penicillin Str.=Streptomycin

(1) *Minor Pyogenic Conditions*

Boils, carbuncles, abscesses, whitlows, infected injuries, &c. These conditions provide a constant stream of surgery attendances. They must be treated with penicillin by injection. My own experience with oral penicillin in these conditions, even in individual doses of two million units, has been extremely disappointing, apart from the occasional mild case in a child. A high blood penicillin level is necessary to ensure penetration of the antibiotic into the localized inflammatory focus.

There are two alternatives: Aqueous sodium penicillin G in twelve- or twenty-four-hourly dosage or a long-acting repository preparation. Over the past seven years I have treated the majority of these cases with four or five daily injections of 200,000 or 500,000 units of aqueous sodium penicillin G. Surgical intervention is hardly ever necessary although very occasionally an alternative antibiotic has to be used because of the presence of resistant organisms. I give my penicillin by subcutaneous injection, as this is simple, time-saving and painless, particularly in the case of children. A dose of 500,000 units dissolves readily in 1 ml. of sterile water and, apart from occasional transient stinging and slight bruising at the injection site, it is free of side-effects. I have now given many thousands of such injections without any other reaction. Several workers have shown absorption to be exactly the same, if not superior, after subcutaneous injection as after intramuscular injection. Custom dies hard and I believe that in hospital penicillin is still given by intramuscular injection, although with penicillin in its present highly purified state, it is difficult to see the justification for continuing this. Fig. 1 shows a typical result in a case of carbuncle of the neck, using this treatment.

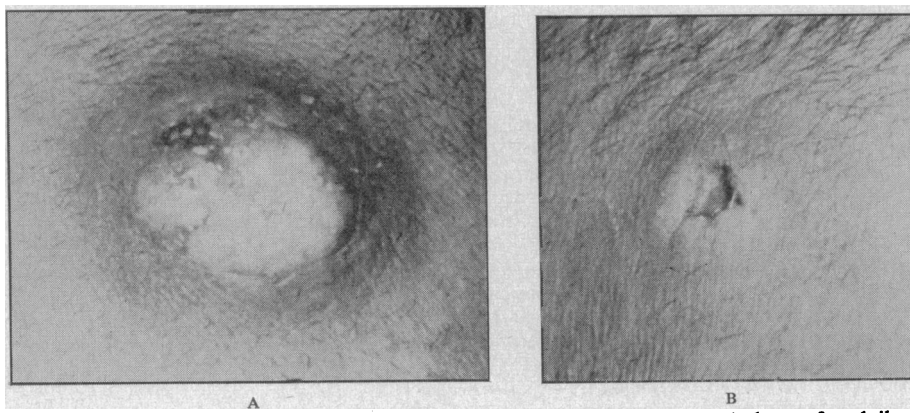

FIG. 1.—First day—before treatment with subcutaneous penicillin. Tenth day—after daily injection of 500,000 units for five days.

Recently I have treated a series of 40 cases, with a single injection of long-acting benethamine penicillin (600,000 units). This has obvious advantages, if equally effective, as it reduces surgery attendances by three-quarters. A disadvantage is the intramuscular injection which in 20% of cases produces pain, sometimes so severe as to incapacitate the recipient for several days. The results too, are less certain. Thus in these 40 cases, there were 10 complete failures, which subsequently responded rapidly to daily aqueous penicillin and 2 cases in which resolution was prolonged. The other 28 cases resolved rapidly in the usual five to eight days. I would like to contrast this with a series which I published in 1949 (*Practitioner*, **162**, 508) of 43 similar cases treated with 4 daily subcutaneous aqueous penicillin injections of 200,000 units. There were no failures, and only one case of delayed resolution.

(2) *Acute Tonsillitis and Pharyngitis*

I treat all these cases with oral penicillin, when they are clearly infective rather than catarrhal. For adults I use 250 mg. (400,000 unit) tablets of unbuffered penicillin G in a standard dose of 2, eight-hourly on an empty stomach. This conveniently fits into the waking day, the first dose being taken before breakfast, the next between 3 and 4 p.m. and the last one on going to bed. I have found from experience that patients with a non-serious condition just will not stick to six- or four-hourly dosage at night. This eight-hourly regime I have found to be entirely effective. Usually there is a striking improvement within eighteen hours with fall of temperature to subnormal and relief of soreness. Occasionally a case fails to respond. This is usually due to infection with a non-sensitive organism and if there is no response within thirty-six hours, therapy should be changed to sulphonamides or Chloromycetin, whilst the result of bacteriological examination is awaited.

In children, it is convenient to use one of the long-acting dibenzyl penicillin suspensions. Their palatability and high concentration (300,000 units/fl. drachm) make them particularly suitable for this purpose. Recently I have been observing the effects of doses given morning and evening only; the dose for 5-year-olds being 600,000 units b.d. So far, in 22 cases exhibiting acute follicular tonsillitis with temperatures in the region of 102–3° F., there has been complete resolution of symptoms and signs in forty-eight hours in every one. Treatment is usually continued for three to four days. Quite apart from the curative effect of such a method, it is very probable that it exerts untold prophylactic benefit in preventing the serious sequelæ of streptococcal infection. Thus in my practice over the last seven years, I have seen no cases of acute rheumatism or acute nephritis and only 3 cases of scarlet fever, all of which had developed before treatment could be instituted.

(3) *Acute Otitis Media*

In contrast to the low incidence of streptococcal allergy in my practice, acute otitis media is extremely prevalent. This occurs either as an acute entity or secondary to untreated throat infection. Often the infection is mixed, and penicillin alone is usually inadequate to deal with it. Oral penicillin, in the doses already outlined, however, may be readily combined with sulphadimidine, also in eight-hourly dosage, and this synergistic combination will deal with the majority of infecting organisms. Thus in a series of 61 cases (*Brit. med. J.*, 1953, i, 806), every case resolved with either oral penicillin or penicillin+sulphadimidine. Oral penicillin alone proved sufficient in the milder cases, in which inflammation and bulging of the tympanic membrane were present, but little constitutional disturbance. In severe cases, with much pyrexia and pain or when perforation had already occurred, the two drugs were given together. Of 29 cases treated with oral penicillin alone, none perforated after treatment was begun and there were no recurrences in the next three months. In one case, chloramphenicol was substituted because of lack of response. Of 32 cases treated with oral penicillin and sulphadimidine combined, 13 had perforated before treatment was begun. All these perforations healed and there were no other instances of perforation. One case suffered a recurrence in three months and in 2 other cases chloramphenicol had to be substituted because of lack of response.

General practice offers unique opportunities for follow-up of these cases, with particular reference to the late effect on hearing. About three-quarters have been observed for periods of two to four years and in none has there been any residual hearing defect, as measured by the ability to hear the whispered voice at 15 feet with the affected ear alone.

Professor L. P. Garrod: My part in this meeting is also to speak on the use, as distinct from the abuse, of antibiotics, and the aspects of this large subject with which I hope to deal can be stated in a few propositions.

The first is that penicillin, when it will serve the purpose, is the antibiotic of choice. The decision to use it is perhaps more easily made than the choice of many forms of this drug which are now available. Sodium penicillin produces high blood levels lasting only a few hours, and procaine, benethamine and benzathine penicillin act respectively for about one,

four and twenty-one days after a single moderate dose, but produce proportionately lower blood levels. A very long-acting form is of obvious value in the prevention of rheumatic fever and in the treatment of highly susceptible infections, such as yaws, in patients who may not return for a second dose. What is much less certain is the relative advantage of high intermittent blood levels or continuous low ones in the treatment of everyday conditions. Some important theoretical considerations involved in this are often overlooked, and the question is not only more complex than is generally thought, but still unsettled.

My second proposition is that, as regards choice of treatment, infections fall into two classes. There are those in which the choice of the antibiotic follows automatically from the diagnosis: these are specific diseases of which the bacterial cause is always the same and always susceptible to the antibiotic in question. They include all characteristic hæmolytic streptococcal infections, syphilis, typhus, typhoid and plague. In the other class are conditions in which the nature of the infection does not follow from the clinical diagnosis, and those, such as a carbuncle, in which it does, but the sensitivity of the organism to a given antibiotic cannot be assumed. In all such patients treatment should if possible be based on bacteriological examination including a sensitivity test; only then can it be pursued with confidence in the result. The chief types of organism whose sensitivity to antibiotics is unpredictable are staphylococci and various Gram-negative bacilli, and the tendency is towards an increasing frequency of strains resistant to any antibiotic which has been in general use for any considerable time.

Of the newer antibiotics two have very restricted but nevertheless valuable uses. Neomycin is generally considered too toxic for parenteral use, but given orally it is preferable to streptomycin for pre-operative suppression of the bowel flora. Its advantages are that bacterial resistance to it is less readily developed, and that in any case such resistance is distinct from that to streptomycin, so that it leaves the field clear for the later use of that drug should it be indicated. If applied to the skin, as it sometimes is, neomycin has the further advantage of not sensitizing the patient to streptomycin. Polymyxin finds its clearest indication in serious infections due to *Ps. pyocyanea*, an organism which is apt to be resistant to all other drugs whatever. *Bact. coli* is also highly sensitive to it, as are other related species. Meningitis due to such organisms can be safely treated by intrathecal, and urinary infections by intramuscular, injections of polymyxin B or E. These two forms of this antibiotic, of the five now known, do not cause renal damage if used in moderation.

Erythromycin has a very similar antibacterial spectrum to that of penicillin, particularly in relation to Gram-positive cocci: their differences in action on certain Gram-negative bacilli are somewhat more pronounced, and the degree of effect against such organisms is, of course, much less. Erythromycin is an easy alternative to penicillin for any pyogenic coccal infection in which penicillin is contraindicated on account of bacterial resistance or sensitivity in the patient. The only infections in which bacterial resistance—not only to penicillin but to the tetracyclines—are likely to call for its use are staphylococcal. In my opinion it should be used with caution and restraint for this purpose, and caution in hospital should go to the length of isolating the patient with a staphylococcal infection as for infectious disease. Resistance to erythromycin can develop rather rapidly, and since this antibiotic is now our last line of defence against staphylococcal infection, every effort should be made to prevent the dissemination of resistant strains.

The latest important antibiotic—tetracycline—is almost indistinguishable from chlortetracycline (Aureomycin) and oxytetracycline (Terramycin) in its antibacterial action: such superiority over them as it possesses depends on a lesser liability to cause gastro-intestinal disturbance. It seems evident from observations in the U.S.A. that tetracycline less often causes nausea or diarrhœa than either of these other drugs. On the other hand, it is difficult to understand why its use should not sometimes be complicated, as is that of the others, by a fulminating enteritis caused by a staphylococcus resistant to all of them.

My final proposition is that combined treatment is being too freely used. It has several distinct theoretical advantages, but the application of each is limited. Synergism is one, but the synergic action of penicillin and streptomycin is therapeutically essential perhaps only in endocarditis due to *Str. fæcalis*. Some combinations are actually antagonistic, and clear clinical proof of this has been obtained in the much inferior results when chlortetracycline was given in addition to penicillin in pneumococcal meningitis. The combination most commonly used, because it has been widely advertised as a commercial product, is that of penicillin and streptomycin. The great majority of patients to whom this has been given would have done equally well with penicillin only, and there are several good reasons why streptomycin should not be employed except for clear indications.

Dr. Lindsey W. Batten: I take it that by "abuse of antibiotics" we mean "misuse" and that we are concerned with well-intended but harmful employment of these agents. Every abuse of antibiotics contravenes at least one of three principles or rules of good practice.

Toxicity.—The first is not to hurt or endanger our patients—*primum non nocere!* It is certain that many patients have been hurt—some mortally—by antibiotics and I am sure that many patients and some doctors are unconscious of the risks they take when they receive or give these things. We here know that all antibiotics except penicillin can be toxic (though you would never think so from the advertisements). We can deduce that on this particular count penicillin is best and that antibiotics, like sulphonamides, are, in general, short-term, and not long-term remedies. There I will leave toxicity—perhaps the least disturbing of the dangers, for other things that *can* happen are quite terrifying.

May I briefly recall a few recent happenings, courageously reported in the recent literature?

On March 27, tetracycline got this modest welcome in an Annotation (*Lancet*, 1954). "It is valuable to have a broad-spectrum antibiotic which seems to cause unpleasant side-effects so seldom". On May 8, Hay and Mackenzie (1954) reported the deaths of two young children from fulminating staphylococcal gastro-enteritis on the fifth and sixth days of treatment with oxytetracycline (Terramycin). One, a girl of 6, was a salmonella carrier but "physically well" when treatment began; the other, a boy of 2, was recovering from a mild diarrhœa believed, on indirect evidence, to be Sonne dysentery. These tragedies and misadventures are disturbing enough but in our daily practice the use of oxytetracycline, at least for minor illness, should not be hard to avoid. It is otherwise with penicillin which, I am sure, has seemed to most of us until quite lately surprisingly safe. It is not so.

Last January R. C. Bell (1954) reported two sudden deaths and some near-fatal anaphylactic reactions after what was at least meant to be intramuscular injection of procaine penicillin. A child of 3½ received one dose safely but died two and a half hours after the second injection next day. The condition for which it was given is not reported.

A man with thrombophlebitis had a severe anaphylactic reaction after Distaquaine—given once before with a mild reaction. His life was saved with adrenaline but it was a near thing. Other similar cases, very alarming to read, are reported in the same communication.

Nor is it always procaine penicillin. A man with a stricture was given, as prophylaxis, a dose of penicillin G before a bougie was passed. He had had many such injections safely before—some trouble once with procaine penicillin—but this last injection proved fatal.

Quite lately W. J. S. Still (1954) reported from Durham the case of a young woman of 28 who was given 300,000 units of crystalline penicillin by injection for a small whitlow in the second day of her puerperium. Twenty-four hours later, besides pain, redness and swelling at the site of injection, she had symptoms as of "acute abdomen". Laparotomy disclosed 6 in. of small bowel, dark purple and apparently becoming necrotic. This was resected and after a stormy post-operative period with severe anaphylactic phenomena in many parts of the body she recovered. After—but not before her injection was given— it was discovered that she had reacted unfavourably to penicillin some years before. Still gives references to fatal anaphylactic reactions reported in the *British Medical Journal* by various authors in 1951, 1952 and 1953.

One case of another kind was reported by S. G. Browne (1954). Briefly, a patient in the Congo with amœbic hepatitis received, in addition to the specific treatment for amœbic infection, a total of 6½ million units of penicillin. On the last day of his penicillin he began a moniliasis of the air- and food-passages which refused to be subdued either in Africa or in London and was still active four years later.

Though these happenings are obviously not cases of abuse they are clear evidence that the antibiotics, emphatically including penicillin, are dangerous—far more likely to end a life suddenly and unintentionally than most of the drugs in the schedules of the D.D.A. To employ them without recognizing this fact, to give them without all reasonable and practicable precautions is, I suggest, to abuse them.

What can be done to prevent recurrence of such incidents?

Hay and McKenzie (1954) most reasonably suggest that "Broad spectrum antibiotics should not be used in minor illness". If a healthy child's bowel cannot be cleared of salmonella or Sonne by safer means, well, carry them she must. If I can find no other way to rid a young woman of axillary boils than to give her the erythromycin which alone controls her staphylococcus, then I must urge her to put up with them. (In parenthesis, judicious X-rays cured her.) Procaine penicillin may get into veins by mistake, though it seems pretty certain that this is not always the cause of the trouble. Bell, Rannie and Wynne (1954) suggest means to reduce the risk, not elaborate but hard to use invariably in busy general practice. Without going all the way we could, I think, always inject into the upper buttock and always leave the needle in situ for some seconds after the stab, to make sure no blood comes out through it, before we attach the charged syringe.

We must always ascertain our patient's previous experience of penicillin before we inject it; have adrenaline or antihistamines handy and, I suggest, use no procaine penicillin if crystalline will serve and no antibiotic if sulphonamides will do as well. We should think twice about giving the "first ever" dose of penicillin—in itself the safest of all but possibly

sensitizing. The "penicillin umbrella" should be reserved for real impending storms and not unfurled and hoisted at every threatened shower.

Wastage.—Some may say that wasting is merely an economic sin. I cannot agree.

Economy—the nice adjustment of means to ends—pertains, I am sure, to the καλὸν κ'ἀγαθὸν—the beautiful and good. Waste, its opposite, pertains to the ἀιοχρόν και κακόν—the ugly and bad. I can adduce no evidence that antibiotics *are* wasted.

The Medical Research Council (1954) published the results of a trial of systemic antibiotics in certain dermatoses. The substances included Aureomycin, chloramphenicol and Terramycin and they proved useless for herpes simplex recurrens, dermatitis herpetiformis, pityriasis rosea, lichen planus, discoid eczema and plantar warts. I cannot believe the M.R.C. would have conducted this research had not many practitioners thought these might possibly be of benefit. Chloramphenicol has no effect on whooping cough after the first week and it has no very startling effect even then. Its occasional use may be justifiable but I feel myself that even if it could not cause aplastic anæmia the use as a palliative of so very costly a remedy in an illness often no worse than a nuisance comes perilously near to abuse.

Then there is oral penicillin. Anyone who dislikes stabbing children must want to believe in its efficacy but the finding of Fairbrother and Daber (1954) last April that "absorption was irregular irrespective of the nature of the compound and the age of the recipient" rings true to me and I cannot help thinking it is abuse on the score of waste and futility to give it as a first dose in acute infection and doubtful practice to give it to adults at all.

Penicillin lozenges I think may constitute an abuse by merely existing.

The third, most subtle and, in the long run, probably worst abuse is queering the pitch for our successors—or even for ourselves if we go on playing. Those deadly staphylococci, those monilia in permanent possession of the field are not pirates or privateers accidentally encountered, they are detachments of an army. They are also portents.

We were scoffed at long since for "pouring medicines of which we know little into bodies of which we know less". Browne (1954), reporting the moniliasis, remarks: "one of the risks of using antibiotics is that their selective action may disturb the bacterial equilibrium of the gut or lung".

There are parallels in agriculture.

We plough the fields and scatter insecticides and selective weed-killers on the land and we find we have killed birds, bees and flowers who minister in various ways to our health and happiness and with whom we have no quarrel. With a little more knowledge I am sure I could tell you of pests we have unwittingly encouraged. We should study the balance of Nature in field and hedgerow, nose, throat and gut before we seriously disturb it.

Again, we may come to the end of antibiotics. We may run clean out of effective ammunition and *then* how the bacteria and moulds will lord it.

A leader-writer quotes the Mayo Clinic who "wish to emphasize that they do not advocate the use of erythromycin in chronic infections such as osteomyelitis, bacterial endocarditis, &c., because of the strong likelihood of provoking bacterial resistance. They *abhor its indiscriminate use*" (*see Brit. med. J.*, 1954).

"ὁ βίος βραχὺς, ἡ δὲ τέχνη μάκρα" "Life is short but the Art is long."

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Dr. J. D. N. Nabarro: The abuses of antibiotics may be considered under two headings, using them unnecessarily and using them unwisely.

Antibiotics may be regarded as being used unnecessarily when they are given by injection, by mouth, or used as a local application in cases of minor or self-limiting conditions from which a good recovery may be expected without their use. If the antibiotics were completely innocuous drugs with a potentiality only for doing good, the sole objection to their use in minor illnesses would be their cost—admittedly an important consideration in some instances. In fact, however, this is far from the case. There are at least four ways in which the unnecessary use of antibiotics may be harmful to the individual patient, or to the population in general. It may harm the patient by giving rise to undesirable side-effects, it may harm him by interfering with the development of antibodies and it may harm him by sensitizing

him to the antibiotic—so that, at some time in the future when he really does need it, he gets an unpleasant reaction. From the point of view of the population as a whole, the widespread and unnecessary use of antibiotics is most undesirable because it encourages the emergence of resistant strains. Some of these points may be considered in greater detail.

Most doctors have encountered cases in which antibiotics given for minor ailments have given rise to side-effects more troublesome than the original illness. Common examples are, stomatitis following the use of penicillin lozenges, an eczematous reaction produced by a local application of penicillin cream and intractable diarrhœa after a short course of one of the broad-spectrum antibiotics. If these complications occur when the antibiotic is being used for the treatment of a severe illness, they may reasonably be looked upon as part of the price to be paid for recovery. If they follow treatment of a minor ailment, the patient has some justification in claiming that the cure is worse than the disease.

In this country, intramuscular penicillin is looked upon as a form of medication that can be given without fear of untoward side-effects. There is a tendency to give it in borderline cases because it may do some good and cannot do any harm. In contrast to this two recent American views may be quoted. Sheldon Swift (1954) has pointed out that about 10% of outpatients attending a New York hospital are recorded as being sensitive to penicillin, and that anyone who has had a minor reaction to this antibiotic in the past may get a fatal anaphylactic reaction if given an intramuscular injection of it. Barach (1954) regards the dangers of anaphylactic reaction and sudden death following penicillin injections so seriously that he thinks that "perhaps the time has come to limit penicillin by injection to those cases in which exceptionally high blood levels are needed for survival such as subacute bacterial endocarditis". In other cases he would give oral penicillin in coated tablets at a dose of one million units three times a day before meals.

The second danger of using antibiotics unnecessarily—the risk of sensitizing the patient so that when he really does need the drug he gets an unpleasant reaction to it—needs little elaboration. The most troublesome type of sensitization reaction is the eczematous one and this may go on to an exfoliative dermatitis. It usually occurs in patients who have some skin disease and the original sensitization has been produced by local application of an antibiotic ointment or paste. There is a welcome tendency to use for local application antibiotics that are generally regarded as being too toxic for parenteral administration—substances like neomycin and bacitracin.

The most important objection to the use of antibiotics in minor illnesses is the increasing proportion of bacteria found to be resistant after the widespread use of an antibiotic. The staphylococcus is the organism that most easily produces antibiotic resistant strains, and the extent to which this occurs seems to be related to the amount of the antibiotic in general use. This is well brought out in Table I which is derived from data published by Spink (1954) for

TABLE I.—Percentage of staphylococci isolated from patients attending the University of Minnesota clinics resistant to antibiotics. Data derived from: A.M.A., *Arch. intern. Med.*—Spink—Aug. 1954.

	Isolated in		
Resistant to	1951	1952	1953
Penicillin	63%	57%	63%
Streptomycin	48%	49%	65%
Chlortetracycline	23%	33%	63%
Oxytetracycline	38%	48%	63%
Erythromycin	—	0	18%
Chloramphenicol	25%	3%	1%

the resistance of staphylococci obtained in the years 1951 to 1953 from patients at clinics run by the University of Minnesota. Over this period penicillin resistance was steady at about 60%, streptomycin resistance rose slightly. During the years 1951 and 1952, chlortetracycline and oxytetracycline were being used extensively in the U.S.A. and the percentage of resistant organisms rose from 23% and 38% to 63%. In the case of the more recently introduced erythromycin the percentage rose from nil to nearly 20% in the first year. In this country erythromycin should be very useful for treating illnesses due to strains of staphylococci resistant to other antibiotics but if it is used indiscriminately there is little doubt that the percentage of organisms resistant to it will soon rise. The most interesting feature of this table is the virtual disappearance of chloramphenicol-resistant staphylococci. Reports of aplastic anæmia following this antibiotic were published in America in 1952; subsequently very little of it was used and the incidence of resistant strains decreased remarkably. It appears, therefore, that the emergence of resistant strains is closely related to the extent to which an antibiotic is used. The only way to minimize this change in the bacterial population is to cut down as far as possible the amount of antibiotic used and to reserve it for cases in which it is really needed. If we fail to do this, if we continue to

prescribe antibiotics for minor ailments, we may well produce a situation in which all the patients but none of the organisms are sensitive to them.

Turning to the second form of abuse of the antibiotics—using them unwisely, one is concerned with matters of detail rather than general principles. I should like to draw attention to a few points based either on published reports or on personal experience. It is unwise to give streptomycin to a patient with chest disease of uncertain ætiology or pyrexia of unknown origin. If the condition responds to this antibiotic the physician is often left in a quandary. The underlying cause may well have been tuberculosis, in which case streptomycin with supporting chemotherapy should be continued for from three to six months. If the condition is non-tuberculous such prolonged treatment is unnecessary. Care is also needed when streptomycin is given to patients with acute or chronic renal failure. About three-quarters of an injection of streptomycin is excreted in the urine. If it is given in the usual doses to patients with renal failure, very high blood levels may result. There is one report of fatal encephalopathy having been produced in this way (Hunnicutt *et al.*, 1948).

It is not yet possible to say with any certainty what constitutes the unwise use of chloramphenicol. Repeated or prolonged courses may give rise to aplastic anæmia with a high mortality rate, but the incidence of this dramatic complication remains uncertain. The Council on Pharmacy and Chemistry of the American Medical Association (1954) has advised that the use of chloramphenicol should be confined to cases of typhoid fever and other serious infectious illnesses that cannot be treated with any other antibiotic. Under the latter may be included severe infections due to staphylococci resistant to the remaining antibiotics and *H. influenzæ* meningitis. It is worth noting that many of the reported cases have occurred in patients given repeated courses for recurrent urinary tract infections.

An interesting situation arose when chlortetracycline was first introduced. Nausea and vomiting were described as troublesome complications and in the early reports it was claimed that this could be prevented or reduced by the use of aluminium hydroxide gel (Schoenbach *et al.*, 1948). Shortly afterwards, however, it was shown that the aluminium hydroxide interfered with the absorption of chlortetracycline and that when the two were given together the blood levels were less than when the antibiotic was given alone (Waisbren and Hueckel, 1949). A good way of preventing this nausea and vomiting is to give the chlortetracycline with a glass of milk or yoghourt (Barach, 1954).

There is a tendency in hospitals to try combinations of antibiotics, if one alone fails to control an infection. Although there is excellent evidence that penicillin and streptomycin have a synergistic action the important experimental and clinical evidence of antagonism between the broad-spectrum antibiotics on the one hand and penicillin and streptomycin on the other, is often forgotten. Lepper and Dowling (1951) studied 28 patients with pneumococcal meningitis. All were treated with one mega unit of penicillin two-hourly by intramuscular injection and alternate cases in addition received 0·5 gram chlortetracycline intravenously every six hours. The cases were apparently of comparable severity but whereas only 3 of the 14 treated with penicillin alone died, 11 deaths occurred among the 14 given chlortetracycline in addition. This is a striking confirmation of the previously demonstrated action of chlortetracycline interfering with the bactericidal effect of penicillin (Gunnison *et al.*, 1950).

Some of these are admittedly minor abuses of the antibiotics but they are points that can easily be overlooked. By far the greatest dangers are those of widespread sensitization of patients and the development of resistance on the part of the bacteria.

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Dr. John Fry: The use of antibiotics in general practice presents special problems regarding the indications for their use and the methods of their administration.

There is only one absolute indication for the use of these drugs—namely, infection by sensitive organisms. The problems are the accurate clinical diagnosis of these conditions and the proper assessment of each case to decide whether they are really necessary to help the body's natural defences.

In spite of the introduction of the many new antibiotics *penicillin* is still the safest and most useful in general practice. It should be administered by intramuscular injection, when indicated, except in infants. In this way its use will be more restricted to appropriate cases, its effects will be more reliable and it will be the most economical way of administration. When prescribed, it should be administered by the practitioner himself, for in my opinion any case which needs penicillin also requires daily medical supervision.

There are very few indications in general practice for the newer wide-spectrum antibiotics and in many ways it is a pity that the restrictions regarding their use have recently been lifted. There was a lot to be said for the old system whereby their use was restricted to certain specified conditions. In my own practice over a period of one year (1954–5) antibiotic and chemotherapeutic drugs were prescribed to 350 patients out of the 5,000 at risk, indicating the wide uses of these drugs. Tables I and II show the conditions for which they were necessary and the preparations which were used.

TABLE I.—DISEASES REQUIRING ANTIBIOTICS IN ONE YEAR IN A GENERAL PRACTICE

Skin and subcutaneous infections	113	32%
Eye infections	48	14%
Acute chest infections ..	47	14%
Acute throat infections ..	47	14%
Acute otitis media ..	36	10%
Genito-urinary infections	31	9%
Tuberculosis	8	2%
Others	20	5%
	350	100%

TABLE II.—DRUGS USED

Penicillin		273	78%
I.M.	264		
Oral	9		
Local	—		
Sulphonamides		44	12·5%
Chloramphenicol		29	8·5%
Oral	14		
Local	15		
Chlortetracycline (*Aureomycin*)		4	1%
Oral	2		
Local	2		

In general practice it is necessary to use *techniques* which are compatible with the rush and tear in this field. Single daily penicillin injections are therefore needed. I have found that high dosage of procaine penicillin (600,000 units) combined with soluble penicillin (200,000 units) (Abbocillin) is satisfactory. Long courses of penicillin, as recommended by many consultants in hospital practice, seem unnecessary in general practice and in the vast majority of cases, including serious conditions such as pneumonia, the infection can be controlled by as few as one daily injection for four days.

The abuse of antibiotics occurs only in connexion with oral therapy and could be limited if penicillin (by the intramuscular injection) or sulphonamides were used in the first instance and if the following points were borne in mind: (i) antibiotics should never be used without first making a definite diagnosis, (ii) if no clinical response is obvious in forty-eight hours—then the case must be carefully reassessed, and (iii) a more complete knowledge of the natural history of the many common infections will show that they will in many instances clear up without the use of these potent drugs.

We must always remember with respect the wonderful natural defences of the human body.

Dr. Horace Joules advocated sulphonamides alone for cases of acute tonsillitis. These resulted from infection by streptococci in over 90% and the response was excellent. No case of acute rheumatism or nephritis had occurred in the past fourteen years among the nursing staff where such treatment had been given.

Pneumonia, in adults, unassociated with an influenzal epidemic, was best treated initially by these drugs as 95% would respond; for boils he preferred intramuscular penicillin 250,000 units b.d. and streptomycin 1·0 gram b.d. for three to four days. If these tended to recur the source was often to be found in the nose when streptomycin inhalations three times daily for one week would usually cut short the tendency.

Dr. B. W. Lacey (Westminster Medical School): I should like to mention three points which appear important enough to be considered as precepts of antibiotic therapy. The first concerns the use of substances such as streptomycin, and probably erythromycin also, to which most bacteria rapidly develop a high level of resistance. It seems reasonable to make it a rule that these should not be given alone, but always with another drug, so that the chances of a resistant mutant appearing are much reduced. And because resistance to streptomycin, and probably erythromycin too, can be developed by some organisms in less than a day it is probably advisable to saturate the patient with the second drug (usually a sulphonamide or penicillin) beforehand. With streptomycin and erythromycin the infected site should be made alkaline if possible before treatment is started. This applies, of course, mostly to infections of the urinary tract where, for example, alkalinization may increase the activity of streptomycin eightfold or more.

The second is a principle of prophylaxis. I think most people would agree that the dangers of the indiscriminate use of chemoprophylaxis in surgery, or against chest infection, &c., should not lead to a general ban on the use of antibiotics in prophylaxis: the administration of penicillin orally for many years in order to prevent a recrudescence of rheumatic carditis appears entirely justifiable. But as a general rule the drug used in prophylaxis should not be that upon which reliance must be placed if the prophylaxis fails. Professor Garrod and others have drawn attention to the danger of giving penicillin for several days before a tooth extraction to a patient predisposed to subacute bacterial endocarditis. On several occasions this practice has been followed by an endocarditis with a fæcal type of streptococcus, highly resistant to penicillin, which had almost certainly been selectively cultivated in the mouth by the prophylaxis. Probably the best course here is to give one of the tetracyclines not more than twelve hours beforehand.

My third point concerns the use of antibiotics locally. When a substance is known to be highly sensitizing it seems reasonable to make it a rule that only exceptional circumstances can justify its use locally. Although the risk is not inconsiderable with penicillin and sulphonamides, it appears greatest with streptomycin and the use of streptomycin in the nose seems most unwise.

One speaker said that he preferred giving a sulphonamide rather than penicillin to young nurses with streptococcal sore throats. This is a curious choice, for there appear to be three good reasons why, for streptococcal infections in young people, penicillin is preferable and which together form almost a legal obligation to give penicillin rather than a sulphonamide. Firstly, all streptococci playing a part in rheumatic fever are believed to be sensitive to penicillin (and never develop resistance) whereas many, or even most in some environments, are comparatively resistant to sulphonamides. Secondly, the toxicity of effective penicillin therapy is unquestionably much less than that of any sulphonamide. Lastly, there is a delay of eight hours or longer before sulphonamides begin to be effective, whereas penicillin acts very rapidly. But in these infections the object of chemotherapy differs from that in, for example, scrub typhus. With streptococcal infections in young people one wants to abolish the infection entirely, as soon as possible, in order to reduce to a minimum the subsequent development of tissue toxic antibodies, whereas in rickettsial infections some immunity mechanism is desirable to eradicate the infection and immediate therapy may lead to a recrudescence.

Although almost all speakers here agree that penicillin should not be used for treating simple boils, I think they have only mentioned giving X-rays or doing nothing as alternatives. But autogenous vaccine with toxoid offers a fair chance, perhaps four to one, of a lengthy remission or complete cure and, with a six-months history, the unpleasantness of the complaint far outweighs that of the inoculations.

My last point refers to the use of antibiotics in virus diseases. There are only a few human diseases undoubtedly caused by viruses or virus-like microbes which are susceptible to chemotherapy. These are: psittacosis, trachoma, inclusion conjunctivitis or urethritis, and lymphogranuloma venereum. They all belong to one, clearly defined, biological group which taxonomists are beginning to regard as rickettsial. For therapeutic purposes, at least, it seems an advantage to accept this, for it makes possible the waste-saving generalization that no human virus disease is casually treatable at present with any chemical. Extravagant claims by manufacturers of antibiotics might then yield less profit and raise fewer false hopes.

Sir Henry Cohen: We should keep a sense of proportion. The discussion has been overweighted with the toxic hazards of penicillin, but it should not be forgotten that the sulphadrugs are relatively more toxic. We must not overlook the blood changes, dermatitis, renal lesions and other toxic complications of their exhibition, and their probable role in such collagen disorders as systemic lupus erythematosus and periarteritis nodosa. Penicillin is still most widely used despite the advent of the newer antibiotics. I have been struck by the fact that penicillin is responsible for 50% of the antibiotic bills in every large hospital in my own region, and I have no reason to doubt that these reflect the general picture. Antibiotics can, of course, be abused, both in treatment and in prophylaxis, and there would appear to be risks associated with the indiscriminate use of penicillin "umbrellas" as pre-operative and pre-parturient measures, which should be more widely appreciated.

The physician should ever remain on the alert to perceive the altered clinical picture produced by antibiotic therapy. For example, the eradication of the infective factor in a renal mycotic aneurysm occurring during the course of a subacute bacterial endocarditis, does not of itself remove the damage to the arterial wall. Consequently, the aneurysm may continue to enlarge and unless tackled surgically may rupture with grave consequences. *Primum non nocere* should remain the guiding maxim in antibiotic therapy.